Summer Showcase 2021

Programme

The Centre for Biological Timing

The CFBT is the largest biological timing research community in Europe, with 27 principal investigators, 86 research staff, and 41 graduate students. Led by Professor Robert Lucas, the CFBT brings together world-leading researchers with a multidisciplinary approach to cellular timers and circadian clocks. Our research spans from model organisms and understanding of fundamental cellular events, through to clinical intervention into human diseases. We undertake this research across three major research themes which will be showcased across three afternoons of talks. Registration.

Monday 28th June: Clinical translation and multi-morbidity

Session 1: Clinical translation and multi-morbidity (Moderators: Martin Rutter, Julie Gibbs, Jean-Michel Fustin).

13:00- Opening remarks by Rob Lucas
13:15- Presentation of the Clinical translation and multi-morbidity research area by Martin Rutter
13:30- Louise Hunter: *Does clock protein REVERBα govern metabolic flexibility?*
14:10- Hannah Durrington: *Asthma...just a question of time!*
14:50- Henrik Oster: *Circadian clock-stress crosstalk*
15:30- Closing remarks Julie Gibbs

Tuesday 29th June: Brain, behaviour and environmental response

Session 2: Brain, behaviour and environmental response (Moderators: Tim Brown, Julie Gibbs, Jean-Michel Fustin).

13:00- Opening remarks by Julie Gibbs
13:15- Presentation of the Clinical translation and multi-morbidity research area by Tim Brown
13:30- Nina Milosavljevic: *Tracing ipRGCs projections in the mouse brain*
14:10- Tim Brown: *SCN output-dependent controls on physiological timing*
14:50- Masao Doi: *Time as medicine and disease etiology*
15:30- Closing remarks by Jean-Michel Fustin

Wednesday 30th June: Internal homeostasis and clock mechanisms

Session 3: Internal homeostasis and clock mechanisms (Moderators: David Bechtold, Julie Gibbs, Jean-Michel Fustin).

13:00- Opening remarks by Jean-Michel Fustin
13:15- Presentation of the Internal homeostasis and clock mechanisms research area by David Bechtold
13:30- Qing-Jun Meng: *Circadian rhythms in the musculoskeletal system: implications in tissue homeostasis and ageing*
14:10- David Bechtold: *Rhythmic influences over cardiac conduction and susceptibility to arrhythmia*
14:50- Katja Lamia: *Circadian repressors CRY1 and CRY2 modulate exercise-responsive signaling networks*
15:30- Closing remarks by Andrew Loudon

Organisers: Julie Gibbs and Jean-Michel Fustin

Invited Speakers

Prof Henrik Oster, Institute of Neurobiology, University of Lubeck, Germany

The risk of developing metabolic disorders such as obesity or type-2 diabetes is strongly associated with the prevalence of psychosocial stress. Therefore, an improved understanding of adaptive stress responses and their underlying molecular mechanisms is of high medical interest. In response to an acute stressor, the sympathetic nervous system is activated and the hypothalamus–pituitary–adrenal (HPA) axis releases catecholamines and glucocorticoids into the circulation. Recent data suggest that stress responses are also regulated by the endogenous circadian clock adapting physiology and behavior to the environmental changes brought about by the Earth's rotation around its axis. Thus, the timing of stress may critically affect adaptive responses to and the pathological effects of repetitive stressor exposure. We have studied the role of different tissue clocks on the regulation of HPA axis activity in mice. We further characterized the impact of predictable social defeat stress during daytime versus nighttime on behavioral and metabolic regulation and on HPA axis activity. Together, our data suggest a circadian gating of stress adaptation at the level of the HPA axis with impact on metabolic homeostasis and psychobiological functions.

Prof Masao Doi, Graduate School of Pharmaceutical Sciences, Kyoto University

One of the most important conceptual changes brought about by the analysis of circadian-clock-deficient mice is that abnormalities in the circadian clock are linked not only to sleep arousal disorders, but also to a variety of diseases, including cancer, diabetes, and obesity. Our lab previously identified a link between circadian clock malfunction and salt-sensitive hypertension (Doi et al, Nat Med 2010; Doi et al, JCEM 2014). In the CFBT Seminar, I extend this disease study and will explore the impact of circadian clock on age-associated disorder (Sasaki et al, under review). Apart from this topic, we generated mutant mice carrying a mutation only at the E′-box cis-element in the promoter region of the core clock gene Per2. Although Per2 proteins remain intact, this non-coding E′-box mutation abolishes molecular clock oscillation and renders circadian locomotor activity and body temperature rhythm unstable (Doi et al, Nat Commun 2019). In addition, in the hope of developing drugs that target the central clock neurons in the brain, we are interested in studying GPCR signaling in the SCN, which involves Calcr (Goda et al, Genes Dev 2018), RGS16 (Doi et al, Nat Commun 2011), and Gpr176 (Doi et al, Nat Commun 2016; Wang et al., Sci Rep 2020).

Prof Katja Lamia, Department of Molecular Medicine, Scripps Research Institute, San Diego, California

Regular exercise is among the most important public health approaches to combating disease. Long-term metabolic adaptation to repeated exercise stimuli includes alterations in vascularization, metabolic flux, and storage of substrates like glycogen and lipids. The molecular mechanisms underlying the cumulative response to training are not well understood. We measured sprint exercise capacity in sedentary and trained mice and identified time of day dependent impacts of training, which we used to identify specific

molecular signatures correlated with a greater impact of training to improve performance. Acutely, exercise causes temporary hypoxia in muscles and other organs while cellular oxygen consumption outstrips oxygen uptake. Regular exposure to hypoxia via exercise training stimulates long-term beneficial adaptations, including increased vascularization and enhanced glucose uptake. Other aspects of the acute metabolic response to hypoxia are inconsistent with the enhanced oxidative capacity of trained muscle. And prolonged exposure to hypoxia, for example from high altitude exposure or respiratory disease, leads to poor health outcomes such as loss of muscle mass and pulmonary edema. In addition to hypoxia, intense exercise depletes cellular ATP stores, and activates AMP-activated protein kinase (AMPK). Circadian rhythms modulate both hypoxia and AMPK-responsive signaling. The core clock transcription factors, CLOCK and BMAL1, are homologs of hypoxia inducible factor 1 alpha (HIF1-α). BMAL1 can heterodimerize with HIF1-α and we and others have shown that circadian repressors CRY1 and CRY2 can repress BMAL1/HIF1-α heterodimers. I will discuss our investigations of the influence of CRY1, CRY2, and time of day on responses to exercise training.

Organisers: Julie Gibbs and Jean-Michel Fustin